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From DNA to Spatio-Temporal Order
Is DNA a Read-Only-Memory?

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Abstract

The mechanism of the self-regulation of gene expression in living cells is generally explained by considering complicated networks of key-lock relationships. However, with the network hypothesis alone it is impossible to fully explain the mechanism of self-regulation in life. We propose a hypothesis that the field parameters in cellular environment should play important roles in the mechanism of self-regulation, where the conformational transition of DNA induced by field parameters causes robust on/off regulation.

要旨： DNAに蓄えられている一次元の塩基配列情報に基づいて、時空間四次元の生物の自己発展がいかなるメカニズムで行われているのかは、現在でも壮大な謎である。ここでは、細胞環境を規定している場のパラメータが、DNAの高次構造転移を通して、全無的な遺伝子発現の制御に関わっているとする仮説（場の仮説）を提案する。

Introduction

One of the most fascinating aspects of living things is their ability to develop their own bodies in a self-organized manner. Even simple prokaryotic cells are capable of self-reproduction and self-management to survive. Higher organisms develop from a single fertilized egg. The result is a highly reproducible spatio-temporal arrangement of differentiated cells, including cell division, morphological changes in cells and tissues, locomotion, and apoptosis (programmed cell death). Modern biology has clarified that life is maintained under genetic control, i.e. central dogma. Since the genetic information embedded in DNA is preserved within a certain generation, a crucial problem is how a living system can regulate autonomously using the 'read-only' memory stored as one-dimensional base sequence in DNA.

Crisis in the network hypothesis

The most common concept regarding the mechanism of genetic regulation can be described as follows.[1-4] A protein produced based on the information encoded by a specific gene acts as a control factor in regulating the expression of other genes. For example, the concentration of protein A in a cell determines the rate of production, or gene expression, of protein B. The rate of production of protein C is, then given as a function of the concentration of protein B, the rate on protein D is as a function of the concentration of protein C, and so on. Additional signals

from other cells can also affect the rates of ongoing biochemical reactions. Since regulatory proteins and other chemical factors may act in cooperation with other signals to control many other genes, a complicated network with many branches and loops may be generated. Usually, the kinetics of biochemical reactions, including the rate of production of a protein through gene expression, are interpreted within the framework of a mass-action law. If we assume suitable nonlinearity in the differential equation of each kinetic process in the genetic network, we can describe a rich variety of phenomena that are characteristic of a nonlinear dynamical system, such as multiple basins of attraction, temporal rhythm (limit-cycle oscillation), switching (bifurcation), spatiotemporal structures including a Turing pattern, a spiral wave, chaos, etc.[5] Indeed, several studies have addressed such kinetic networks, and many of them have assumed the presence of cubic nonlinearity[6–10] as the product of the concentration of a promoter (or repressor) and the square of the concentration of a regulator.

Unfortunately, there is a serious problem with this network hypothesis.[11,12] The framework of the mass-action law may be correct, to the extent that we can examine the reaction kinetics in a test tube with a size on the order of cm. In contrast, living cells are typically on the order of μm. In addition, there are thousands of different chemical species in a living cell. For example, human cells contain 30000 genes. It would be unreasonable to expect that there is a sufficient amount of each of the regulatory factors of these 30000 genes in a single human cell on the order of 10 μm to neglect the effect of fluctuation. Actually, several scientists have already noticed the critical effect of such fluctuation on the network hypothesis.[13] Robust on/off switching is difficult to apply under the framework of the network hypothesis. Considering the present state of the modeling of cellular behavior, Brooks claimed that 'we might be missing something fundamental and unimagined in our models of biology'.[11]

On/off Switching in Giant DNA

All living cells on Earth posses giant DNA molecules larger than on the order of mega base pairs, M bp. In humans, the total of the full lengths, or contour lengths, of DNA molecules is about 2 m. Even for bacteria, the contour length is on the order of mm. Such long DNA chains are compacted in an intracellular space on the order of μm. Until the mid-1990's, so-called 'DNA condensation'[14, 15] was considered a cooperative phenomenon with a highly cooperative but continuous transition. Recently, based on the direct measurement of the conformation of single DNA molecules, it has been revealed[16–19] that the transition between an elongated coil state and a folded compact state is largely discrete at the level of individual chains, whereas the physico-chemical properties on an ensemble of chains are always continuous. Thus, a giant DNA molecule larger than several tens of kilo base pairs, kbp, is large enough to exhibit an all-or-none behavior in the folding transition. It has been confirmed that the discrete nature of the folding transition is rather general and independent of the condensing agent.

Cross-Talk Between the Folding Transition of DNA and Environmental Parameters

As noted above, it is evident that giant DNA molecules undergo switching on their conformation. For elongated coil DNAs, aqueous solution is a good solvent because of the high negative charge density along the double-stranded chain. On the other hand, for the folded compact state, almost all of the negative charge on DNA is neutralized due to the association of the phosphate group with a counter cation, which is accompanied by a decrease in free energy due to the decrease in the translational entropy of the counter cation. The large difference in the charge of DNA chains means that a large number of counter ions are absorbed/released together with the folding/unfolding transition, respectively.[16, 18, 20] Recently, it has been shown from *in vitro* experiments that giant DNA molecules undergo an unfolding transition induced by an increase in ATP in the presence of a fixed amount of spermidine, a natural polyamine.[21] A similar unfolding transition is observed[22] with an increase in RNA in the solution, and also with an increase in pH. None of these chemicals show a specific interaction with DNA. Instead, these species exist in cells in rather high concentrations. We would like to regard the concentrations of these abundant, non-specific chemicals as environmental parameters. Since these environmental parameters should be involved in the activity of living cells, it is expected that, in a narrow intracellular space, giant DNA molecules should exhibit cross-talk with regard to their respective conformations through these parameters as mediators.[23]

Higher-Order Structure of DNA vs. Genetic Activity

We would like to propose a scenario in which, with a change in an environmental parameter such as the level of ATP, a certain part of chromatin loosens and allows access to transcriptional machinery. It is also important to indicate the possibility of stepwise unfolding/folding of giant DNA.[20,24] As has been explained already, the switching transition of giant DNA is inevitably accompanied by the release or absorption of a large number of small ions. For a small system such as in the cytoplasmic space, the transition of DNA molecules is expected to proceed in a stepwise manner. Since the scale of the transition in the higher-order structure should be greater than several tens of base pairs, such partial loosening would also be greater than the order of several tens of base pairs. Considering that the sequence of amino acids in a protein corresponds to 100~300 bases, the partial loosening would involve several tens or several hundreds of genes. This suggests that the conformational transition in a certain part of DNA acts as a 'holder' of genetic information. It is natural to consider such a system that regulates a huge amount of genetic information, i.e., 30,000 genes in the case of humans, as a combination of both individual genes and 'holders' for several genes. Since the key-lock relationship between a specific regulatory chemical and a specific DNA domain is a kind of dynamic equilibrium, such regulation would be flexible. On the other hand, since the conformational transition of DNA occurs on a larger scale, it would be applicable for switching on a larger number of genes, such

as in cell differentiation. The regulation with a change in the higher-order structure of DNA corresponds to the function of 're-writable' memory, whereas the one-dimensional base sequence is 'read-only memory'. Recent experimental study has confirmed the on/off switching of the genetic activity accompanied by the folding transition of giant DNA.[25,26]

It may be obvious that living organisms can not maintain life only with the 'read-only memory' embedded as a one-dimensional base sequence in DNA. The concept of a 'field', as described using environmental parameters, may be useful for understanding 'what is life?'

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